TAB A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Pastor et al.	Customer No.	: 21003
Serial No.	: 10/647,739	Confirmation No.	: 4202
Filed	: August 25, 2003	Group Art Unit	: 1614
Examiner	: Anderson, James D.		
For	: THERAPY WITH CANNABINOID COMPOUNDS FOR THE TREATMENT OF BRAIN TUMORS		

DECLARATION OF MANUEL GUZMÁN UNDER 37 CFR 1.132

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, MANUEL GUZMÁN, do hereby declare and state as follows:

1. I am a citizen of Spain and am more than twenty-one years of age.

2. I am currently employed by the School of Chemistry, Complutense University, in Madrid, Spain, as a full professor of Biochemistry and Molecular Biology. I have been a full professor since 2005, and was an associate professor from 1993 to 2005. For the past ten years, I have focused my research on the study of molecular mechanisms of cannabinoid action, with a specific interest towards the effects of such action on cancer cells. I have authored numerous scientific articles as noted on my Curriculum Vitae. A copy of my Curriculum Vitae is attached hereto as Appendix A, and lists 30 recent publications, selected from a list of 100 publications.

3. I am an inventor of the above-noted patent application, and have been asked to comment on the patentability of the presently pending claims of this application.

4. I have read and am familiar with the application as it was filed in the U.S. Patent and Trademark Office (the "USPTO"), the pending claims of the application, and the Office Action mailed by the USPTO on October 12, 2007 in connection with the

application.

5. I understand that the claim of the pending application have been rejected by the Examiner as as obvious under 35 U.S.C. § 103(a) over Sanchez (FEBS Letters, 1998, c.436, p. 6-10) in view of Uesugi (Acta Neuropath., 1998, v. 9, pp. 351-356). I have read and am familiar with these references.

6. I understand that the Examiner has taken the position that Sanchez discloses that THC induces apoptosis in C6 glioma cells. Further, the Examiner asserts that Uesugi teaches the use of a rat glioma cell line (C6) as a rat glioma model. The Examiner contends that based on these teachings, one skilled in the art would be motivated to use THC to treat glioblastomas with a reasonable expectation of success *in vivo* given the teachings with respect to the disclosed *in vitro* teachings.

7. It is my opinion that the Examiner's position is an *ex post facto* analysis. It is my opinion that one skilled in the art would not have had any reasonable expectation of success when applying Δ^8- tetrahydrocannabinol (THC) and Δ^9-THC *in vivo* because it was effective *in vitro* for the following reasons.

8. Brain tumors affecting humans, and in particular glioblastomas, have been clinically resistant to all chemotherapies assayed against them. Therefore, these tumors cannot be treated efficiently with chemotherapeutic agents such as DNA alkylating agents, antimetabolites, cytoskeleton inhibitors or topoisomerase inhibitors, although these compounds inhibit the growth or induce apoptosis in glioma cell lines *in vitro.*[1] Analogously, glioma cell lines are sensible *in vitro* to other treatments such as focal radiotherapy and genetic therapy, although gliomas in human patients are not.

9. Gliomas are highly heterogenic tumors from the molecular, cellular and morphologic point of view, whereas a glioma cell line basically consists of a single homogeneous population of cells.[2] Therefore, while the action of a certain treatment in a glioma cell line *in vitro* is limited in its direct action over such single cell population, the

[1] See References 1-4 on attached *Curriculum Vitae* (CV).
[2] See References 1-3 on attached CV.

effect of said treatment in an *in vivo* glioblastoma may be the result of its combined action against different tumor cell populations (for example, amplifying progenitors, differentiated tumor cells, and cancer stem cells) and non-tumor cell populations (for example, vascular endothelial cells, extracellular matrix fibroblasts, leucocytes infiltrated in the tumor), and against biological interactions established between them, most of which are not present in glioma cell line preparations.

10. The addition of a certain chemotherapeutic agent to a cell culture allows a direct access of the agent into the cells. On the contrary, it is well known that the situation *in vivo* is far more complex, since the pharmacokinetic characteristics (ADMET parameters) of the compound must be appropriate in order to carry out a relevant therapeutic action, for instance, the correct access to the site of action, its reduced toxicity, or its half life in the body.

11. The fact that a certain compound induces apoptosis *in vitro* in a tumoral cell line does not mean that, in a case of inhibiting the tumoral growth *in vivo* the compound acts through the same mechanism. For example, cannabinoids induce apoptosis in cutaneous carcinoma and melanoma cell lines *in vitro* but stops the growth in mice with cutaneous carcinoma (angiogenic inhibition)[3] or cutaneous melonoma (angiogenic inhibition and cell proliferation)[4] by different mechanisms.

12. Therefore, the currently pending method claim for a therapeutic treatment of one or more glioblastomas in a mammal, would not be obvious to one skilled in the art. There would be no basis to assume that the teachings of Sanchez in view of Uesagi would render the present claim obvious.

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[3] See Reference 5 on attached CV.
[4] See Reference 6 on attached CV.

13. I hereby declare that all statements herein are based on information and belief and are believed to be true and that these statements were made with the knowledge that willful false statements made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.

Date: February 25, 2008

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ABBREVIATED CV - BIOSKETCH

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PhD Biochemistry, Complutense University, Madrid, Spain, 1990

PREVIOUS RESEARCH/PROFESSIONAL EXPERIENCE

1983-86	Assistant student	Complutense University, Madrid, Spain
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1991-93	Research fellow	Utrecht University, The Netherlands
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1994-2005	Associate Professor	Complutense University, Madrid, Spain

SCIENTIFIC BIOGRAPHY
Manuel Guzmán took his BSc (1986) and PhD (1990) in Biology from Madrid Complutense University. Subsequently he performed his postdoctoral research at the University of Utrecht (The Nertherlands) and the Hannah Research Institute (Ayr, United Kingdom). He is presently Full Professor of Biochemistry and Molecular Biology at Madrid Complutense University. His PhD and postdoctoral research focused on the regulation of fatty acid metabolism. During the last ten years he has been mostly involved in the study of the molecular mechanisms of cannabinoid action, with especial emphasis on how cannabinoids induce cancer-cell death and exert anti-tumor effects, and how cannabinoids modulate neural cell proliferation, differentiation and survival. These studies have allowed the characterization of new effects and signaling pathways coupled to cannabinoid receptors, and overall support the notion that cannabinoids impact very basic processes involved in the control of neural cell fate.

SELECTION OF 30 RECENT PUBLICATIONS
(from approximately 100 total publications)

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11. Casanova, L., Blázquez, C., Fernández-Aceñero, M.J., Villanueva, C., Huffman, J., Jorcano, J.L. & Guzmán, M. (2003) *Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors.* J. Clin. Invest. 111, 43-50.
12. Guzmán, M. (2003) *Cannabinoids: potential anticancer agents.* Nat. Rev. Cancer 3, 745-755.
13. Blázquez, C., Casanova, L., Planas, A., Gómez del Pulgar, T., Villanueva, C., Fernández-Aceñero, M.J., Aragonés, J., Huffman, J., Jorcano, J.L. & Guzmán, M. (2003) *Inhibition of tumor angiogenesis by cannabinoids.* FASEB J. 17, 529-531.
14. Guzmán, M., Lo Verme, J., Fu, J., Oveisi, F., Blázquez, C. & Piomelli, D. (2004) *Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor PPAR-α.* J. Biol. Chem. 279, 27849-27854.
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